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IMMUNE REGULATION

Overcoming T_{Reg}-cell blockade

Evidence has accumulated over the past few years in support of the idea that innate signals mediated by Toll-like receptors (TLRs) influence adaptive responses by inducing dendritic-cell (DC) maturation. This results in upregulation of the expression of MHC and co-stimulatory molecules by DCs. Now, Chandrashekhar Pasare and Ruslan Medzhitov report that TLR signals can influence adaptive responses through a second, distinct mechanism — by blocking the suppressive effects of regulatory T (T_{Reg}) cells on effector T cells.

The authors set out to test the hypothesis that T_{Reg} cells might be regulated by TLR signals. CD4⁺CD25⁺ T_{Reg} cells can suppress the activation of CD4⁺CD25⁻ T cells in the presence of immature splenic DCs. When the DCs were stimulated using lipopolysaccharide (LPS, which targets TLR4) or CpG DNA (which targets TLR9), they upregulated their expression of MHC class II and co-stimulatory molecules, and T_{Reg}-cell-mediated suppression of effector T-cell activation was abrogated.

This effect seems to be independent of co-stimulation as MyD88-deficient DCs — which can upregulate expression of co-stimulatory and MHC class II molecules, but cannot induce cytokine production — are unable to block suppression mediated by T_{Reg} cells. When conditioned medium (CM) from activated DCs was added to the T_{Reg} assays, suppression was blocked, which indicates that soluble mediators are responsible for the effect.

Does the soluble mediator target the T_{Reg} cells directly or does it make the effector T cells unresponsive to suppression? Exposure of T_{Reg} cells to CM from TLR-stimulated DCs before adding them to the T_{Reg} assay had no effect, which indicates that a cytokine present in the CM makes the effector T cells unresponsive to suppression by T_{Reg} cells.

So, what is the cytokine that mediates this suppressive effect? Using various methods, the authors ruled out roles for interleukin-2 (IL-2), IL-7 and IL-15. Using size-exclusion chromatography combined with ELISA of fractions of CM, IL-6 was identified as a strong candidate. CM from LPS-treated IL-6-deficient mice could not suppress the effect of T_{Reg} cells on effector T cells. But, addition of IL-6 alone to these cells did not restore suppressive activity, which indicates

that another cytokine might act in synergy with IL-6 in this system.

Together, these results indicate a second mechanism by which TLR signals influence adaptive immune responses — production of IL-6 by DCs renders effector T cells unresponsive to suppression by T_{Reg} cells. The authors suggest that this mechanism is crucial for generating protective responses during infection, as it allows pathogen-specific T cells to subvert the suppressive effects of T_{Reg} cells.

Elaine Bell

References and links

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FURTHER READING Medzhitov, R. Toll-like receptors and innate immunity. *Nature Rev. Immunol.* 1, 135–145 (2001)

WEB SITE

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http://info.med.yale.edu/immuno/fac_medzhitov.html